PATENT SPECIFICATION 808,105

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COMPLETE SPECIFICATION.

New Pharmaceutical Compositions.

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

This invention relates to new pharmaceutical compositions and more particularly it relates to ointments, creams and pastes possessing antimycobacterial activity and suitable for application to the skin.

We have found that particular solid formulations for example formulations in the form of creams, ointments or pastes containing certain thiol esters as active ingredients, are suitable for administration by infracation into the skin and when so administered, the active ingredient is absorbed through the skin and thereby exerts its antimycobacterial for example antituberculosis action. In United Kingdom Patent Specification No. 746,051 there are described and claimed pharmaceutical compositions effective in the treatment of tuberculosis wherein the active ingredient is S : S¹-diethyldithiolterephthalate. In United Kingdom Patent Specification No. 758,464 there are described and claimed pharmaceutical compositions effective in the treatment of tuberculosis wherein the active ingredient comprises one or more compounds of stated formula for example diethyl dithiolisophthalate in proportion between 10% and 80% by weight of the compositions. Neither of these Specifications discloses the pharmaceutical compositions of the present invention nor is there any suggestion in them that antitubercular activity may be obtained by application to the skin of the active ingredient or ingredients as pharmaceutical compositions in the form of ointments, creams or pastes.

Thus according to the invention we provide pharmaceutical compositions which are ointments, creams or pastes wherein the active ingredient is a compound of the formula :—

R—COSEt

wherein R stands for an ethylthio radical or for a phenyl radical which may optionally be substituted by an ethylthiocarbonyl radical.

Suitable compounds of the above stated formula may be for example diethyl dithiolcarbonate, ethyl thiolbenzoate, diethyl dithiolphthalate, diethyl dithiolisophthalate and diethyl dithiolterephthalate and of these, diethyl dithiolisophthalate is preferred.

It is to be understood that the said ointments, creams and pastes are suitable for administration by direct application to the skin and when so administered, the active ingredient is absorbed in a sufficient amount to be able to exert its required systemic effect. The selection of suitable pharmaceutical excipients is therefore dependent upon the physical properties of the active ingredient which may be for example in the form of a solid or a liquid.

Solid active ingredients for example diethyl dithiolterephthalate may be dispersed in ointment bases or in emulsified bases known as creams. We prefer to use those bases which are known to promote the absorption of medicaments through normal skin. Suitable substances capable of being absorbed through the skin may be for example animal or vegetable fats and oils for example castor oil, arachis oil, coconut oil or lanolin, derivatives thereof such as the corresponding higher aliphatic and olefinic acids for example

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Price 4s 6d.

EXAMPLE 2.

A mixture of 12 parts of stearic acid and 25 parts of castor oil at 60—65° C. is added to a solution of 1 part of triethanolamine and 52 parts of water at 60—65° C. The mixture so obtained is emulsified and added in portions to 10 parts of finely ground diethyl dithiolterephthalate. There is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 3.

A mixture of 20 parts of arachis oil and 10 parts of stearyl alcohol at 65—70° C. is added with stirring to 70 parts of diethyl ditholcarbonate at 65—70° C. The mixture is then stirred and cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 4.

A mixture of 20 parts of diethyl dithiolcarbonate, 14 parts of cetostearyl alcohol and 6 parts of arachis oil is added at 60—65° C. to a solution of 2 parts of Cetomacrogol 1000 B.P.C. in 58 parts of water at 60—65° C. The mixture so obtained is emulsified and homogenised and there is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 5.

25 parts of magnesium stearate are added to 75 parts of diethyl dithiolcarbonate and the mixture thus obtained is a medicated paste which is suitable for application to the skin.

EXAMPLE 6.

60 parts of starch are added to 40 parts of diethyl dithiolcarbonate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 7.

55 parts of bentonite are added to 45 parts of diethyl dithiolcarbonate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 8.

A mixture of 25 parts of castor oil and 5 parts of beeswax at 65—70° C. is added with stirring to 70 parts of ethyl thiolbenzoate at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 9.

A mixture of 25 parts of ethyl thiolbenzoate, 12 parts of cetyl alcohol and 8 parts of coconut oil is added at 60—65° C. to a solution of 0.5 part of cetrimide in 54.5 parts of water at 60—65° C. The mixture so obtained is emulsified and homogenised and there is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 10.

30 parts of aluminium monostearate are added to 70 parts of ethyl thiolbenzoate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 11.

A mixture of 25 parts of cetyl alcohol and 15 parts of glyceryl monostearate at 65—70° C. is added with stirring to 60 parts of diethyl dithiolisophthalate at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 12.

A mixture of 20 parts of soft paraffin and 20 parts of cetostearyl alcohol at 65—70° C. is added with stirring to 60 parts of diethyl dithiolisophthalate at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 13.

A mixture of 7 parts of lanolin, 8 parts of cetyl alcohol, 5 parts of arachis oil and 60 parts of diethyl dithiolisophthalate at 60—65° C. is diluted by slowly stirring in 20 parts of water at 60—65° C. There is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 14.

To a stirred mixture of 15 parts of cetyl alcohol and 65 parts of diethyl dithiolisophthalate at 65—70° C. are added 20 parts of calcium oleate. The mixture is then cooled and there is thus obtained a medicated paste suitable for application to the skin.

EXAMPLE 15.

57 parts of starch are added to 43 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 16.

30 parts of kaolin are added to 70 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 17.

25 parts of zinc stearate are added to 75 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 18.

30 parts of magnesium stearate are added to 70 parts of diethyl dithiolisophthalate and

16. Compositions as claimed in Claim 15 wherein the known additional ingredient is *iso*nicotinic acid hydrazide.

17. Pharmaceutical compositions, claimed in Claims 1—16, as hereinbefore particularly described and especially with reference to the foregoing Examples 1—20.

ALFRED O. BALL,
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PROVISIONAL SPECIFICATION.

New Pharmaceutical Compositions.

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare this invention to be described in the following statement :—

This invention relates to new pharmaceutical compositions and more particularly it relates to ointments, creams and pastes possessing antituberculosis activity and suitable for application to the skin.

In our co-pending Application No. 33935/53 there are disclosed pharmaceutical compositions which are liquid compositions, suitable for parenteral administration in the treatment of tuberculosis, containing certain thiol esters.

We have now found that particular solid formulations for example formulations in the form of creams, ointments or pastes containing certain of these thiol esters as the active ingredient, are suitable for administration by infrication into the skin and when so administered, the active ingredient is absorbed through the skin and thereby exerts its antituberculosis action.

Thus according to the invention we provide new pharmaceutical compositions which are ointments, creams or pastes wherein the active ingredient is a compound of the formula

R—COSEt

wherein R stands for an ethylthio radical or for a phenyl radical which may optionally be substituted by an ethyl thiocarbonyl radical.

Suitable compounds of the above stated formula may be for example diethyl dithiolcarbonate, ethyl thiobenzoate, diethyl dithiolphthalate, diethyl dithiolisophthalate and diethyl dithiolterephthalate.

It is to be understood that the said ointments, creams and pastes are suitable for administration by direct application to the skin and when so administered, the active ingredient is absorbed in a sufficient amount to be able to exert its required systemic effect. The selection of suitable pharmaceutical excipients is therefore dependent upon the physical properties of the active ingredient which may be for example in the form of a solid or of a liquid.

Solid active ingredients for example diethyl dithiolterephthalate may be dispersed in ointment bases or in emulsified bases known as creams. We prefer to use those bases which are known to promote the absorption of medicaments through normal skin. Suitable substances capable of being absorbed through the skin may be for example animal or vegetable fats and oils for example castor oil, arachis oil, coconut oil or lanolin, derivatives thereof such as the corresponding higher aliphatic and olefinic acids for example stearic acid, palmitic acid or oleic acid and the related alcohols for example cetyl alcohol, stearyl alcohol, cetostearyl alcohol and wool alcohols.

The emulsified bases or creams which may be used for incorporation of the active ingredient are oil-in-water or water-in-oil type emulsions of the above materials optionally containing other excipients suitable for the provision of stable emulsions of the requisite physical form. Any type of emulsifying agent known to the art may be used provided that it does not promote decomposition of the active ingredient or delay absorption of the active ingredient through the skin. As suitable emulsifying agents there may be mentioned for example salts of fatty acids for example salts of stearic acid with alkali metal bases for example sodium hydroxide or with organic bases for example triethanolamine, or combinations of fatty alcohols for example cetyl alcohol, stearyl alcohol and cetostearyl alcohol with long chain quaternary ammonium salts for example cetrimide or mixtures thereof or with sulphated fatty alcohols for example dodecyl sulphate or their salts for example sodium dodecyl sulphate and triethanolamine dodecyl sulphate or polyoxyethylene ethers of fatty alcohols or polyoxyethylene esters of fatty acids.

The compositions may contain additional excipients such as thickening agents especially in the formulation of ointment compositions. Suitable thickening agents may be for example higher paraffinic hydrocarbons for example soft paraffin and spermaceti and beeswax.

Liquid active ingredients for example diethyl dithiolcarbonate, ethyl thiolbenzoate and diethyl dithiolisophthalate may be incorporated into the above described ointment bases or the emulsified bases for example

parts of beeswax at 65—70° C. is added with stirring to 70 parts of ethyl thiolbenzoate at at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 9.

A mixture of 25 parts of ethyl thiolbenzoate 12 parts of cetyl alcohol and 8 parts of coconut oil is added at 60—65° C. to a solution of 0.5 part of cetrimide in 54.5 parts of water at 60—65° C. The mixture so obtained is emulsified and homogenised and there is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 10.

30 parts of aluminium monostearate are added to 70 parts of ethyl thiolbenzoate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 11.

A mixture of 25 parts of cetyl alcohol and 15 parts of glyceryl monostearate at 65—70° C. is added with stirring to 60 parts of diethyl dithiolisophthalate at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 12.

A mixture of 20 parts of soft paraffin and 20 parts of cetostearyl alcohol at 65—70° C. is added with stirring to 60 parts of diethyl dithiolisophthalate at 65—70° C. The mixture is then cooled and there is thus obtained a medicated ointment suitable for application to the skin.

EXAMPLE 13.

A mixture of 7 parts of lanoline, 8 parts of cetyl alcohol, 5 parts of arachis oil and 60 parts of diethyl dithiolisophthalate at 60—65° C. is diluted by slowly stirring in 20 parts of water at 60—65° C. There is thus obtained a medicated cream suitable for application to the skin.

EXAMPLE 14.

To a stirred mixture of 15 parts of cetyl alcohol and 65 parts of diethyl dithiolisophthalate at 65—70° C. are added 20 parts of calcium oleate. The mixture is then cooled and there is thus obtained a medicated paste suitable for application to the skin.

EXAMPLE 15.

57 parts of starch are added to 43 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 16.

30 parts of kaolin are added to 70 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

EXAMPLE 17.

25 parts of zinc stearate are added to 75 parts of diethyl dithiolisophthalate and the mixture thus obtained is a medicated paste suitable for application to the skin.

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